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Cost–Utility Analysis of Topical Intranasal Steroids for Otitis Media with Effusion Based on Evidence from the GNOME Trial

Stavros Petrou, PhD,[1,2] Helen Dakin, MSc,[1] Giselle Abangma, MSc,[1] Sarah Benge, PhD,[3] Ian Williamson, MD, MRCGP, FRS[3]

[1]Health Economics Research Centre, Department of Public Health, University of Oxford (Old Road Campus), Headington, Oxford, UK; [2]National Perinatal Epidemiology Unit, Department of Public Health, University of Oxford (Old Road Campus), Headington, Oxford, UK; [3]Primary Medical Care, University of Southampton, Aldermoor Health Centre, Southampton, UK

ABSTRACT

Objectives: To estimate the cost-effectiveness of topical intranasal steroids for the treatment of otitis media with effusion (OME) in primary care from the perspective of the UK National Health Service.

Methods: An economic evaluation was conducted based on evidence from the double-blind, randomized, placebo-controlled GPRF [General Practice Research Framework] Nasal Steroids for Otitis Media with Effusion (GNOME) trial. Participants comprised 217 children aged 4–11 years who had at least one episode of otitis media or related ear problem in the previous 12 months and had tympanometrically confirmed bilateral OME. Children were randomly allocated to receive either mometasone furoate 50 μg or placebo spray once daily into each nostril for 3 months. The main outcome measure was the incremental cost per quality-adjusted life-year (QALY) gained for topical steroids compared with placebo. The nonparametric bootstrap method was used to present cost-effectiveness acceptability curves at alternative willingness to pay thresholds.

Results: Children receiving topical steroids accrued nonsignificantly higher costs (incremental cost/child: £11, 95% confidence interval [CI]: –£199 to £222) and nonsignificantly fewer QALYs (incremental QALY gain/child: –0.0166, 95% CI: –0.0652 to 0.0320) than those receiving placebo. Topical steroids had a 24.19% probability of being cost-effective at a £20,000 per QALY gained threshold, a 23.82% probability of being more effective and a 46.25% probability of being less costly. Sensitivity and subgroup analyses showed incremental costs and benefits to be highly sensitive to the methods used and the patient group considered, although differences between groups did not reach statistical significance in any analysis.

Conclusions: Topical steroids are unlikely to be a cost-effective treatment for OME in general practice.

Keywords: cost-effectiveness, cost-utility analysis, otitis media with effusion, randomized controlled trial.

Introduction

Otitis media with effusion (OME) has been defined as the presence of fluid in the middle ear without signs or symptoms of acute ear infection [1]. Epidemiological studies of OME reveal that it affects 50–80% of children by the age of five [2,3]. Without effective intervention, severe OME can cause significant hearing loss, which may result in linguistic, developmental, behavioral, motor, and social impairment [4]. Although many OME cases resolve spontaneously, referral rates from primary care remain high, with approximately 1–5 per 1000 children in the general population undergoing surgery (grommets) each year [5]. A recent review by the National Institute for Health and Clinical Excellence (NICE) revealed that grommets are a cost-effective treatment for children with recurrent otitis media, particularly for older children [6].

Many nonsurgical treatments, such as decongestants, antihistamines, antibiotics, mucolytics, steroids, and autoinflation, are currently used in the UK National Health Service (NHS) as short-term treatments for OME in an attempt to avoid unnecessary secondary referral and costly surgery [7–10]. However, there is little evidence that these nonsurgical options are beneficial [11]. Of the pharmacological nonsurgical treatments currently provided, further evaluation of topical intranasal corticosteroids is particularly warranted as evidence of their efficacy is limited to small clinical trials [12–14] and theoretical benefits, such as shrinkage of peritubal lymphoid tissue or encroaching adenoidal tissue that improves tubal function [15,16]. This further evaluation should aim to estimate the cost-effectiveness of topical intranasal corticosteroids in order to provide decision-makers with evidence on whether the considerable resources currently being invested in this area represent an efficient use of scarce public resources.

A companion paper and a Health Technology Assessment monograph report the methods and results of a recent large double-blind, randomized, placebo-controlled trial GPRF [General Practice Research Framework] Nasal Steroids for Otitis Media with Effusion (GNOME) that compared topical intranasal corticosteroids with no active treatment in children with bilateral OME [17,18]. This paper summarizes the methods and results of an economic evaluation that was based on evidence from the GNOME trial. To our knowledge, it represents the first trial-based economic evaluation of topical intranasal corticosteroids for the treatment of OME in primary care.

Methods

Trial Background

The GNOME study (NRR N0575123823) was a placebo-controlled, double-blind, randomized trial of 217 children aged 4–11 years who had a history of otitis media and tympanometrically confirmed bilateral OME [17,18]. Participating children were recruited from 76 Medical Research Council (MRC) General Practice Research Framework (GPRF) practices throughout the United Kingdom between 2004 and 2007. They

Address correspondence to: Stavros Petrou, National Perinatal Epidemiology Unit, University of Oxford (Old Road Campus), Old Road, Headington, Oxford OX3 7LF, UK. E-mail: stavros.petrou@npeu.ox.ac.uk

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were randomly allocated to receive either 50 μg mometasone furoate nasal spray ($n = 105$) or placebo nasal spray ($n = 112$) once daily in each nostril for 3 months. The primary clinical outcome measure was the proportion of children cured of bilateral OME using tympanometric criteria at one month (i.e., the proportion of children with at least one ear with an A or C1 type recording). Secondary clinical outcome measures included: tympanometric cure 3 and 9 months postbaseline; OM8-30 scores [19] 3 and 9 months postbaseline; and diary-based symptoms, including adenoidal symptoms, snoring, nasal blockage, and rhinorrhoea, recorded weekly over the first 3 months. Ethical approval for the trial was granted by the Metropolitan Multicentre Research Ethics Committee. Further details of the trial, its sampling procedures, methodology, outcome measures and response rates are reported in the companion paper and project monograph [17,18].

Type of Economic Evaluation, Study Perspective and Time Horizon

The economic evaluation took the form of a cost–utility analysis and its primary outcome comprised the incremental cost per quality-adjusted life-year (QALY) gained through using topical steroids in place of no active treatment. The QALY, a preference-based measure that captures gains in both length and health-related quality of life, is the preferred measure of health outcome by decision-making bodies such as NICE [20]. Based on recommendations for technology appraisal [20], a UK NHS perspective was adopted. The analysis took a 9-month time horizon, which equated to the follow-up period used in the trial.

Measurement of Resource Use

Data were collected about all significant health service resource inputs over the 9-month time horizon. Study data forms provided a record of: consultations with community health-care providers; prescribed medications; investigative tests; and hospital inpatient and outpatient service use, for which the length of stay or consultation, reasons for admission or appointment, any operations carried out, the name of the hospital provider, its location, and the ward or clinic attended were recorded. These data were obtained through two principal means. First, research nurses employed through the MRC GPRF retrospectively extracted resource use data from children's general practice (GP) medical records. Second, parents completed health service resource utilization questionnaires at 3 and 9 months. Comparisons of the two sets of resource use data suggested that parents tended to underestimate resource use. Subsequently the resource use data extracted from medical records were used in the base case analysis.

Valuation of Resource Use

Unit costs were obtained from a variety of secondary sources. Resource use valuation followed recent guidelines on costing health services for economic evaluation [19]. Hospital admissions, outpatient consultations, and community health services were valued using national sources, such as NHS Reference Costs [21,22] or local provider tariffs, and took account of the cost of health professionals' qualifications where applicable. Drug costs were obtained from the prescription cost analysis database [23] and British National Formulary [24]. Costs for individual preparations were used as well as costs for chemical entities (i.e., drugs were grouped by chemical entity and the unit costs for these chemical entities were calculated). The unit costs for the most commonly used resources are shown in Table 1 and reported in full in the project monograph [18]. All costs are expressed in UK pounds sterling and valued at 2006–2007 prices. Unit costs were combined with resource volumes to obtain a total cost per

Table 1 Resource use, costs (£) and utility scores per child over the nine-month trial period based on complete case analysis

	Topical steroids		Placebo		Difference		
	Mean	SD	Mean	SD	Mean	SE*	*P**
Resource use based on retrospective review of medical records (unit cost per resource input; N = 100 for topical steroids and 107 for placebo)							
No. GP surgery contacts (£31 [22])	1.67	1.75	1.98	2.03	0.30	0.26	0.252
No. GP home visits (£69 [22])	0.01	0.10	0.01	0.10	0.00	0.01	0.962
No. GP telephone consultations (£27 [22])	0.08	0.31	0.10	0.53	0.02	0.06	0.704
No. GP out of hours consultations (£69 [22])	0.16	0.47	0.08	0.30	0.09	0.06	0.121
No. practice nurse contacts (£29 [22])	0.38	0.81	0.44	0.86	0.06	0.12	0.611
No. practice nurse telephone consultations (£10 [22])	0.03	0.17	0.07	0.29	0.04	0.03	0.275
No. district nurse home visits (£23 [22])	0.00	0.00	0.00	0.00	0.00	0.00	0.000
No. health visitor contacts (£35 [22])	0.04	0.28	0.07	0.37	0.03	0.05	0.577
No. speech therapist contacts (£40 [22])	0.03	0.17	0.03	0.17	0.00	0.02	1.00
No. contacts with other community professionals (£29.29 to £362.05 [21,22])	0.07	0.36	0.03	0.17	0.04	0.04	0.288
No. hospital outpatient referrals (£29.29 to £246.00 [21,22])	0.53	0.77	0.47	0.66	0.06	0.10	0.563
No. hospital admissions (£458.49 to £2997.20 [21])	0.18	0.54	0.24	0.47	0.06	0.07	0.230
No. investigative tests (£1.45 to 19.22 [21])	0.03	0.17	0.09	0.32	0.06	0.04	0.075
Costs (£, based on retrospective review of medical records; N = 100 for topical steroids and 107 for placebo)							
Hospital outpatient costs	54.49	83.38	53.66	80.41	0.83	11.40	0.942
Hospital inpatient costs	280.98	767.06	288.39	611.11	7.40	96.82	0.939
Community health service costs	92.92	136.90	95.44	99.26	2.51	16.72	0.881
Medication costs excluding mometasone	6.04	13.23	11.09	27.32	5.05	2.95	0.089
Topical mometasone	15.66	0.00	—	—	—	—	—
Total healthcare costs including mometasone	450.09	842.79	448.57	647.29	1.52	104.97	0.988
Utilities							
HUI3 utility							
Baseline (N = 63 for steroids, 69 for placebo)	0.777	0.211	0.779	0.241	–0.002	0.039	0.959
3 months (N = 56 for steroids, 54 for placebo)	0.804	0.229	0.877	0.171	–0.073	0.038	0.060
9 months (N = 56 for steroids, 54 for placebo)	0.880	0.208	0.881	0.189	0.000	0.038	0.996

*Standard errors and *P*-values were calculated in Microsoft Excel 2003 using two-tailed Student's *t*-tests assuming unequal variance.
HUI, Health Utilities Index; N, number of children with data; SD, standard deviation; SE, standard error around the mean.

child covering all categories of hospital and community health services.

Calculation of Health Utilities and Quality-Adjusted Life-years (QALYs)

Health utilities were measured using the Health Utilities Index (HUI) [25] and the EuroQol EQ-5D [26] multiattribute utility measures. The HUI was introduced into the GNOME study following a protocol amendment that occurred after 33.2% (72/217) of the children had been recruited, in order to allow cost–utility analysis to be conducted. Parents completed the unedited 15-item questionnaire for proxy-assessed usual health status assessment, which was obtained from the HUI developers and covers both HUI2 and HUI3 health status classification systems. Standard multiplicative multiattribute utility functions for the HUI2 and HUI3 (based on a visual analogue scaling technique and a standard gamble instrument [27,28]) were used to calculate utilities. The EQ-5D questionnaire [26] was also introduced following the protocol amendment. Both questionnaires were completed at baseline, 3 and 9 months.

The base case analysis used HUI3 utilities as the HUI3 is now recommended by the HUI developers because of its broad applicability in both clinical and general population health studies, improvements in several definitions, and increased orthogonality of its attributes for structural independence [29]. Additionally, the HUI3 contains separate attributes for hearing and speech and may therefore be more sensitive to small differences in OME severity than the HUI2 or EQ-5D.

Because preliminary analyses highlighted an imbalance in baseline utility values between study arms, we adjusted each child's utility scores by subtracting their baselines utility score from their Utility scores at 3 and 9 months postrandomization, so that each on-treatment measurement indicates the increase (or decrease) in utility from baseline [30]. The number of QALYs gained/lost relative to baseline was calculated as the area under the baseline-adjusted utility curve, assuming linear interpolation between the three utility measurements.

Methods for Dealing with Missing Data

Multiple imputation [31,32] was used to impute missing data and avoid biases associated with complete case analysis [31]. Missing data was a particular issue for utility scores. However, although no utility data were available for children recruited early in the trial, utility scores were found to correlate well [33] with the scores on the disease-specific OM8-30 questionnaire [19] that were available for most children. Consequently, multiple imputation took account of the predicted HUI3 utility scores that were estimated using a mapping algorithm developed using the GNOME trial data that predicts children's HUI3 utility scores based on OM8-30 facet scores [33].

The "ice" command within Stata (Version 10.0; Stata Corp, College Station, TX) [34] was used to impute missing data for the following variables: log-transformed total cost based on data from medical records and that from parental questionnaires; log-transformed disutilities at baseline, 3, and 9 months using the HUI3, HUI2, and EQ-5D measures; predicted HUI3 utilities at baseline, 3, and 9 months estimated using the OM8-30 mapping equation [33]; and whether OME was cured at either 1 or 3 months. Age, sex, and treatment allocation were included as additional explanatory variables in the imputation models. The "match" option within "ice" was used for disutilities and costs as this algorithm is less dependent on assumptions of normality than default options. Five imputed datasets were generated. Imputed values were transformed back to a natural scale where required.

Cost-Effectiveness Analytical Methods

Independent-sample *t*-tests were used to test for differences in resource use, costs, utility scores, and QALYs between treatment groups. All statistical tests were two-tailed.

The five imputed datasets generated through multiple imputation were bootstrapped [35] separately in Microsoft Excel 2003 (Microsoft Corporation, Redmond, WA) and the results were combined using equations described by Briggs et al. [31] to calculate standard errors around mean costs and effects that incorporate uncertainty around imputed values as well as sampling variation. Standard errors were used to calculate 95% confidence intervals (CIs) around total and incremental costs and QALYs based on Student's *t*-distribution.

Cost-effectiveness acceptability curves [36], showing the probability that topical steroids are cost-effective relative to no active treatment at a range of ceiling ratios were generated based on the proportion of bootstrap replicates (across all five imputed datasets) with positive incremental net benefits [37]. Incremental net benefit was defined as the incremental QALY gain multiplied by the ceiling ratio minus the incremental cost [37], where the ceiling ratio (or threshold) represents the maximum society is willing or able to pay for each additional QALY. Unless otherwise stated, all statements about cost-effectiveness are based on a £20,000 per QALY gained threshold [20]. The probability that topical steroids are less costly or more effective than no treatment was based on the proportion of bootstrap replicates that had negative incremental costs or positive incremental QALYs, respectively. In order to assess the value of collecting further information and quantifying the consequences of the uncertainty around the decision, we also estimated the expected value of perfect information (EVPI), which reflects the theoretical maximum amount that we should consider spending on further research that would eliminate all decision uncertainty [38]. The EVPI per child was estimated by subtracting the total net benefit for the option we would choose based on current information from the maximum net benefit we would obtain with perfect information (the average of the maximum net benefit for each bootstrap replicate). No discounting was applied to costs and health effects as the time horizon for the economic evaluation was less than 1 year.

Several sensitivity analyses [36] were undertaken to assess the impact of areas of uncertainty surrounding components of the economic evaluation. These included: 1) basing costs on responses to parental questionnaires; 2) basing the economic evaluation on a complete case analysis; 3) basing utilities on the HUI2 measure; 4) basing utilities on the EQ-5D measure; and 5) making no adjustment to baseline utilities. Results were also calculated for subgroups of children stratified by key characteristics: 1) age (<6.5 years, ≥6.5 years); 2) gender (boys, girls); 3) atopy (yes, no); 4) baseline clinical severity score (upper quartile [severe disease], children with less severe disease); 5) month of recruitment (January–March, April–December); and 6) period of trial recruitment (prior to protocol amendment described above, following protocol amendment). All subgroup analyses were post hoc.

Results

The main clinical results of the trial are presented in the companion paper and project monograph [17,18]. In brief, 40.6% (39/96) of the topical steroid group and 44.9% (44/98) of the

Table 2 Costs (£), utilities and quality-adjusted life-years (QALYs) per child over the nine-month trial period, including values imputed using multiple imputation

	Topical steroids (N = 105)		Placebo (N = 112)		Difference		
	Mean	SE[†]	Mean	SE[†]	Mean	SE[‡]	*P*[§]
Total cost (£)							
Medical records	453.54	82.14	442.31	61.84	11.23	101.85	0.912
Parents' questionnaires	458.31	97.80	273.60	60.84	184.71	121.33	0.129
HUI3 utilities							
Baseline	0.758	0.044	0.766	0.758	–0.008	0.034	0.815
3 months	0.776	0.061	0.836	0.776	–0.060	0.034	0.073
9 months	0.876	0.027	0.871	0.876	0.004	0.037	0.908
HUI2 utilities							
Baseline	0.849	0.027	0.855	0.849	–0.006	0.027	0.831
3 months	0.890	0.031	0.901	0.890	–0.011	0.022	0.627
9 months	0.919	0.017	0.897	0.919	0.022	0.022	0.323
EQ–5D utilities							
Baseline	0.884	0.039	0.913	0.884	–0.029	0.036	0.424
3 months	0.937	0.019	0.917	0.937	0.021	0.024	0.402
9 months	0.928	0.024	0.923	0.928	0.004	0.034	0.904
Unadjusted QALYs							
HUI3	0.605	0.031	0.627	0.605	–0.023	0.018	0.218
HUI2	0.670	0.015	0.669	0.670	0.001	0.012	0.943
EQ–5D	0.694	0.012	0.689	0.694	0.005	0.015	0.735
Baseline-adjusted QALYs							
HUI3	0.036	0.018	0.053	0.036	–0.017	0.024	0.480
HUI2	0.033	0.012	0.028	0.033	0.005	0.016	0.737
EQ-5D	0.031	0.022	0.004	0.031	0.027	0.022	0.220

[†]Standard errors were calculated across all five imputed datasets using methods described previously [31].
[‡]$SE^2_{difference} = SE^2_{Treatment} + SE^2_{placebo}$.
[§]Based on a two-tailed *t*-test conducted in Microsoft Excel 2003 whereby t equaled mean divided by standard error and p was calculated based on the t-distribution in Excel.
HUI, Health Utilities Index; QALY, quality-adjusted life year; SE, standard error.

placebo group achieved tympanometric cure (C1 or A type) in one or both ears at 1 month (adjusted odds ratio: 0.934, 95% CI: 0.498–1.751, $P = 0.831$). There were no significant differences between the two groups in any secondary outcomes at 1, 3, or 9 months.

Health Service Resource Use and Costs

Resource use data from medical records were available for 95% (207/217) of the children (Table 1). There was no significant difference between the groups for any category of health service resource use or costs ($P > 0.05$). Overall, this population of children with OME managed in primary care attended an average of 1.83 (standard deviation [SD]: 1.90) GP consultations in the 9-month study period. Based on cases with complete cost data, the total cost of managing children randomized to topical steroids was £450.09 per child over the 9-month study period, compared with £448.57 per child for the placebo group ($P = 0.60$). Although only 19% (39/207) of children were admitted to hospital, inpatient care accounted for 63% of total costs, with each hospital admission costing an average of £284.80 (SD: £689.16).

Although the complete case analysis (Table 1) suggested that use of topical steroids increased total costs by just £1.52 per child ($P = 0.99$), the incremental cost per child rose to £11.23 ($P = 0.91$) when missing cost data were estimated using multiple imputation and all children were included in the analysis (Table 2).

Health Utilities

Because of the late introduction of multiattribute utility measures and noncompletion of questionnaires, 94% (202/216) of HUI3 utility measurements for children recruited before the protocol amendment and 22% (97/435) of those for children recruited after the protocol amendment were missing. Utility scores were similar across the two study groups and there was no significant difference between groups in HUI3 utility scores at any time point. However, both groups showed an increase in utility score from an overall mean HUI3 utility score of 0.778 (SD = 0.226, N = 132) at baseline to 0.840 (SD = 0.205, N = 110) at 3 months and 0.880 (SD = 0.198, N = 110) at 9 months (complete case analysis). Children achieving tympanometric cure at 3 months had a mean HUI3 utility score of 0.854 (SD = 0.193, N = 63) at this time point, compared with 0.828 (SD = 0.202, N = 42) for children not achieving tympanometric cure ($P = 0.516$; complete case analysis).

Both mapping techniques and multiple imputation suggested that those children with missing utility data had slightly lower utility scores than those with complete data; imputing missing data therefore reduced mean utilities slightly (Tables 1 and 2). However, there was no significant difference in health utilities between the study groups regardless of the methodology used.

In the base-case analysis, which includes both baseline adjustment of utility scores (subtracting baseline utility from on-treatment utility scores) and multiple imputation, children randomized to topical steroids accrued 0.017 fewer QALYs than those randomized to placebo ($P = 0.48$; Table 2).

Cost-Utility Analysis

The base-case analysis suggested that, on average, topical steroids were dominated by no active treatment, costing an additional £11.23 (bootstrap 95% CI: –£199.14 to £221.60), with a net loss of 0.017 (–0.032–0.065) QALYs per child treated (Table 3). However, there is substantial uncertainty around this finding. Based on the distribution of bootstrap replicates, there is a 46% probability that treating children with topical steroids would accrue lower costs than no active treatment, as well as a 24% probability that active treatment would generate more QALYs. The probability of topical steroids being cost-effective

Table 3 Incremental cost-effectiveness ratios for the base-case analysis and sensitivity analyses

Analysis	Mean costs (95% CI)			Mean QALYs gained relative to baseline utility (95% CI)			Cost/QALY (£)	Probability active treatment is		
	Active (£)	Placebo (£)	Difference (£)	Active	Placebo	Difference		Cost-effective (%)*	More effective (%)	Less costly (%)
Base-case†	454 (284, 623)	442 (314, 571)	11 (−199, 222)	0.036 (−0.001, 0.074)	0.053 (0.019, 0.086)	−0.017 (−0.065, 0.032)	Dominated (−676)	24.19	23.82	46.25
Resource use based on parental data‡	458 (253, 663)	274 (149, 398)	185 (−69, 438)	0.036 (−0.002, 0.074)	0.053 (0.019, 0.087)	−0.017 (−0.065, 0.032)	Dominated (−11,115)	14.08	24.22	4.72
Complete case analysis§	550 (300, 801)	352 (190, 513)	199 (−99, 497)	0.041 (0.011, 0.072)	0.047 (0.016, 0.079)	−0.006 (−0.050, 0.038)	Dominated (−33,504)	25.30	40.20	9.50
Utilities derived from HUI2‡	454 (287, 620)	442 (315, 570)	11 (−197, 219)	0.033 (0.008, 0.058)	0.028 (−0.008, 0.064)	0.005 (−0.028, 0.038)	2,161	63.20	65.72	47.16
Utilities derived from EQ-5D‡	454 (284, 623)	442 (317, 568)	11 (−199, 222)	0.031 (−0.018, 0.079)	0.004 (−0.023, 0.030)	0.027 (−0.019, 0.073)	418	88.66	89.22	46.88
No adjustment for baseline utilities‡	454 (282, 625)	442 (314, 570)	11 (−199, 221)	0.605 (0.524, 0.685)	0.627 (0.552, 0.702)	−0.023 (−0.060, 0.015)	Dominated (−499)	11.64	10.28	46.68

*Treatment was considered to be "cost-effective" if it had positive net benefit at a £20,000/QALY ceiling ratio.
†Based on 5000 bootstrap replicates for each of the five imputed datasets.
‡Based on 1000 bootstrap replicates for each of the five imputed datasets.
§Complete case analysis included placebo N = 52; active treatment N = 52; 1000 bootstrap replicates were simulated for a single dataset that excludes missing values.
CI, [bootstrap] confidence interval; HUI, Health Utilities Index; QALY, quality-adjusted life-year.

compared with no active treatment was found to be 24.2% at a £20,000 per QALY threshold, and 23.9% at a £30,000 per QALY threshold (Fig. 1).

EVPI was found to equal £65.73 per child or £9.1 million for the 160,000 children in the United KIngdom who would be potentially eligible for treatment over the next 10 years based on the recruitment rate observed at the 76 GP practices participating in GNOME (discounted at 3.5% per annum). EVPI reflects the theoretical maximum that it would be cost-effective to spend on further research that would eliminate all uncertainty around the decision. In this case, the EVPI is higher than the cost of many trials, which suggests that it may be cost-effective to collect further evidence on the efficacy and cost-effectiveness of steroids for OME. However, optimal decisions regarding future research would need to also take account of the costs of research and the extent to which any given trial would reduce the chance and cost of making the wrong decision.

Sensitivity Analyses

Sensitivity analyses explored the impact of varying the methods and values used in the economic evaluation (Table 3, Fig. 1). Basing health service resource use estimates on parental questionnaires rather than medical records reduced mean costs in the placebo group by 44%, increased the incremental cost of topical steroids to £185 (bootstrap 95% CI: –£69 to £438) per child and decreased the probability that treatment is cost-effective at a £20,000 per QALY threshold to 14%.

Conducting a complete case analysis on 104 out of the 217 children with complete cost and utility data substantially increased incremental costs and benefits, although topical steroids remained dominated by no active treatment with a 25% chance of being cost-effective.

However, based on HUI2 utilities, the average child receiving topical steroids accrued 0.005 (–0.028–0.038) more QALYs than those receiving no active treatment, giving an incremental cost per QALY gained of £2161. Although this point estimate would be considered cost-effective, if society were willing to pay £20,000 for an additional QALY, uncertainty around costs and benefits meant that the probability of treatment being cost-effective was 63%. Similarly, when the EQ-5D instrument was used, the incremental cost per QALY gained was estimated at £418 and steroids were found to have an 89% probability of being cost-effective at a £20,000 per QALY threshold. Finally, not adjusting for baseline utility slightly increased the QALY loss from treatment and reduced the probability of treatment being cost-effective to 12%.

Subgroup Analyses

Total and incremental costs and QALYs attributable to topical steroids differed substantially between patient subgroups (Table 4). Total costs were lower in the treatment group than the placebo group for six of the 12 subgroups investigated, with the largest savings occurring in older children and those with less severe disease. By contrast, the treatment group accrued fewer QALYs than the placebo group in all 12 subgroups. Overall, there were no subgroups in which the probability of cost-effectiveness exceeded 45% at the £20,000 per QALY threshold.

Discussion

The study reported in this paper represents a comprehensive economic evaluation of topical intranasal steroids for the treatment of 4–11-year-old children with OME in primary care. It represents, to our knowledge, the first economic evaluation of

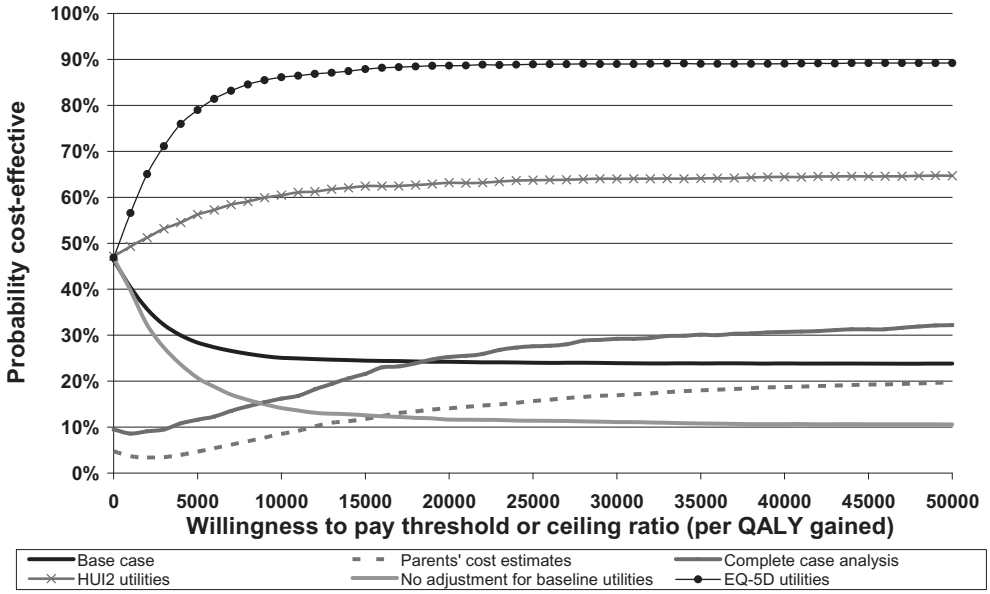

Figure 1 Cost-effectiveness acceptability curves for the base-case analysis and sensitivity analyses. QALY, quality-adjusted life-year.

topical steroids for children with OME. The economic evaluation was conducted according to nationally agreed design and reporting guidelines [20,39]. It was based on the largest double-blind, randomized, placebo-controlled trial of topical steroids in children with OME in any health setting, and larger than the only previous randomized control trial from primary care which evaluated antibiotic use for this condition [40]. The GNOME trial enabled collection of a broad range of resource use, clinical effectiveness, and health utility data that may inform future economic evaluations of other OME interventions. Moreover, the costing analysis was rigorous and included all significant resource items calculated from a health service perspective.

The economic evaluation found that topical steroids are unlikely to be a cost-effective treatment for OME in this primary care population and (based on current evidence) there are no grounds for adopting mometasone as a treatment for OME in this patient group. The cost–utility analysis showed active treatment to be dominated by no active treatment, costing an additional £11 and producing 0.017 fewer QALYs per child treated (on average), although treatment groups did not differ significantly in either costs or benefits. Moreover, this conclusion remained relatively robust in sensitivity analyses that accounted for the uncertainty surrounding components of the economic evaluation. Furthermore, subgroup analyses demonstrated that active treatment may cause harm in some subgroups: there was a 72% probability that topical steroids would reduce the number of QALYs accrued in older children (≥6.5 years) and an 83% probability in children with severe disease.

A number of caveats should be noted when interpreting the study results. First, the method of recruitment into the GNOME study, which included formal audits by research nurses with invitations for tympanometric screening [17,18], is likely to have more accurately identified a population for treatment than is usually the case in primary care. This may limit the generalizability of the study findings to actual practice where treatments may be given with less certainty of accurate diagnosis. Nevertheless, additional analyses showed that the study population had presented to their GP with an otitis media or ear problem episode, on average, on two occasions in the previous year, which is typical of primary care practice [11]. In addition, comparisons of the characteristics of the GNOME study population with those from other studies, including the Trial of Alternative Regimens in Glue Ear Treatment (TARGET) trial and Eurotitis samples, revealed that the GNOME study population did not differ significantly in terms of baseline OM8-30 scores [41].

Second, the economic evaluation used a 9-month time horizon based on the study follow-up period. Although topical steroids were only given for 3 months, NHS resource use and health consequences may have extended beyond the end of the treatment because of incomplete resolution of OME and relapse. The 9-month time horizon used in the economic evaluation is likely to have captured all relevant health service resource use and health consequences; the absence of significant differences in costs or health outcomes over the 9-month period suggests that long-term extrapolation would not have affected the findings.

Third, by adopting the recommended NHS perspective [20], the economic evaluation excluded wider costs, such as costs borne by other sectors of the economy, parents, informal carers, and employers. This was primarily the result of preliminary research we had conducted, which suggested that accurate measurement of non-NHS costs would have required far more research intensive involvement with parents during the follow-up period. Our preliminary research suggested that this may have affected response rates to the parental questionnaires, thereby diluting the overall credibility of the study findings. Given the nonsignificant study findings for the primary and secondary clinical outcomes, it is unlikely that including non-NHS costs would have affected the study conclusions. Nevertheless, OME as a condition may lead to costs to education services, personal and social services, parents, informal carers, and employers that future economic evaluations in this area should consider, at least within sensitivity analyses.

Fourth, the base-case cost–utility estimates in the study were based on HUI3 utility scores derived from questionnaires completed by parents. Recent methodological guidance in England and Wales recommends that health-related quality of life should

Table 4 Incremental cost-effectiveness ratios for subgroup analyses

	Mean costs (95% CI)			Mean QALYs gained relative to baseline utility (95% CI)			No. children†			Probability active treatment is		
Subgroup*	Active (£)	Placebo (£)	Difference (£)	Active	Placebo	Difference	Active	Placebo	Cost/QALY (£)	Cost-effective (%)‡	More effective (%)	Less costly (%)
Children ≥6.5 years	260 (114, 405)	412 (222, 601)	−152 (−382, 79)	0.043 (−0.004, 0.090)	0.066 (−0.002, 0.134)	−0.023 (−0.102, 0.056)	37	38	6,611 (SW)	35.06	28.22	90.38
Children <6.5 years	559 (313, 805)	458 (301, 615)	101 (−185, 387)	0.032 (−0.018, 0.082)	0.046 (0.010, 0.082)	−0.014 (−0.067, 0.040)	68	74	Dominated (−7,422)	25.50	30.02	24.96
Boys	527 (267, 786)	465 (299, 630)	62 (−241, 365)	0.045 (−0.008, 0.098)	0.062 (0.001, 0.123)	−0.017 (−0.089, 0.056)	52	63	Dominated (−3,686)	27.62	30.10	34.52
Girls	382 (169, 595)	414 (232, 595)	−32 (−311, 247)	0.028 (−0.045, 0.100)	0.041 (−0.021, 0.103)	−0.014 (−0.081, 0.053)	53	49	2,322 (SW)	35.46	32.26	60.64
Atopy	449 (163, 735)	398 (229, 567)	51 (−259, 361)	0.038 (−0.019, 0.095)	0.053 (−0.003, 0.110)	−0.015 (−0.100, 0.070)	35	33	Dominated (−3,341)	34.02	35.18	39.38
No atopy	456 (248, 664)	461 (305, 616)	−5 (−265, 255)	0.035 (−0.009, 0.079)	0.053 (0.012, 0.093)	−0.017 (−0.069, 0.034)	70	79	286 (SW)	24.82	24.32	51.20
Severe (clinical severity score > 0.62)	586 (248, 924)	442 (220, 664)	145 (−260, 549)	0.020 (−0.077, 0.117)	0.074 (0.007, 0.141)	−0.054 (−0.182, 0.074)	23	23	Dominated (−2,690)	14.46	16.76	24.62
Nonsevere (clinical severity score ≤ 0.62)	367 (167, 566)	460 (300, 619)	−93 (−345, 159)	0.037 (−0.002, 0.077)	0.051 (0.005, 0.096)	−0.013 (−0.065, 0.038)	65	75	7,074 (SW)	37.62	30.34	76.46
Season 1: enrolled January–March	451 (207, 694)	326 (203, 448)	125 (−150, 400)	0.043 (0.003, 0.084)	0.053 (0.005, 0.102)	−0.010 (−0.073, 0.053)	42	44	Dominated (−12,451)	31.04	37.90	17.16
Season 2: enrolled April–December	456 (232, 679)	518 (334, 702)	−62 (−354, 229)	0.031 (−0.027, 0.090)	0.052 (0.008, 0.096)	−0.021 (−0.089, 0.047)	63	68	2,963 (SW)	30.30	25.86	67.26
Early trial period with active monitoring	417 (133, 701)	566 (331, 802)	−149 (−523, 224)	0.021 (−0.084, 0.126)	0.033 (−0.032, 0.098)	−0.012 (−0.114, 0.089)	35	37	12,249 (SW)	44.48	38.00	78.76
Later trial period without active monitoring	472 (266, 677)	381 (249, 513)	91 (−154, 335)	0.044 (0.014, 0.073)	0.062 (0.024, 0.100)	−0.019 (−0.066, 0.028)	70	75	Dominated (−4,838)	17.36	21.10	24.20

*All analyses shown in this table were based on 1000 bootstrap replicates for each of the five imputed datasets.
†Subgroup analyses omit any children with missing data on the parameter used to define the subgroup but include those children with imputed values for costs or quality of life.
‡Treatment was considered to be "cost-effective" if it had positive net benefit at a £20,000/QALY ceiling ratio.
CI, [bootstrap] confidence interval; HUI, Health Utilities Index; QALY, quality-adjusted life-year; SW, south-west quadrant of the cost-effectiveness plane (ICERs in the SW quadrant indicate that active treatment is less costly and less effective than placebo and ICERs *lower* than the ceiling ratio should be considered not cost-effective, because they indicate that the savings are not sufficiently large to warrant the number of QALYs that would be lost).

normally be measured directly by patients themselves using the EQ-5D multiattribute utility measure [20]. At the outset of the study, it was felt that younger children in the GNOME sample would lack the comprehension level required for the available multiattribute utility measures and that parental measurement would be required [42,43]. Moreover, the available psychometric evidence suggested that the HUI3 has greater construct and empirical validity than the EQ-5D in childhood [42–44]. Furthermore, post hoc analyses on the GNOME data suggested that the HUI is more sensitive to differences in tympanometric cure in our study population than the EQ-5D (details available upon request). Consequently, the conclusions for the economic evaluation should, in our opinion, primarily be based on the HUI3-derived incremental cost-utility estimates.

Finally, and related to the fourth caveat, there is a more general concern about the psychometric properties of all the available multiattribute utility measures when applied to children as young as 4 years of age, of which there were some in our study population. Researchers have previously noted that there are likely to be dimensions of health status relevant to young children not reflected by the available multiattribute utility measures [42]. Until the recommended multiattribute utility measures reflect health experiences across all age groups, health economists are likely to continue to rely on the available, but constrained, measures for the purposes of economic evaluation.

In conclusion, our study suggests that topical intranasal corticosteroids are unlikely to be a cost-effective treatment for OME in general practice. However, value of information analysis suggests that future research in this area may be cost-effective. Data on the costs and health-related quality of life of children with OME that were collected in our study may be used to inform future economic evaluations and other empirical research studies in this area.

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